Allergen Immunotherapy

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Allergen immunotherapy plays an important role in the treatment of allergic diseases and asthma. This article is a brief review of the current approaches, including patient and allergen selection, routes of administration, and use of standardized allergen vaccines. New approaches offering potentially useful strategies based on recent studies of T-cell epitopes, cytokines, and anti-IgE and DNA vaccines also are considered.

Introduction

Allergen immunotherapy for the treatment of allergic disease has been practiced since the beginning of the 20th century, based on the pioneering clinical work of Noon [1] and Freeman [2] with allergic rhinitis. Immunotherapy quickly became a major treatment modality, as there was no alternative to offer allergic patients. The acceptance of immunotherapy for the treatment of allergic disease varies among physicians. For example, it would be difficult to deny immunotherapy to patients with life-threatening insect venom hypersensitivity with demonstrable allergen-specific IgE, given the safety, efficacy, and cost of venom immunotherapy. For allergic rhinitis and asthma, immunotherapy traditionally has been an adjunct to environmental control and pharmacologic treatment. Environmental control is, in most cases, the first line of treatment for animal dander allergy and pharmacotherapy for allergic rhinitis and asthma. Immunotherapy generally is felt to be indicated for patients with evidence of a clinically relevant IgE-mediated disease and in whom environmental control and pharmacotherapy are insufficient. According to the National Institutes of Health Expert Panel Report 2, Guidelines for the Diagnosis and Management of Asthma [3], immunotherapy may be considered for asthma patients when 1) there is clear evidence of a relationship between symptoms and exposure to an unavoidable allergen to which the patient is sensitized, 2) symptoms are persistent, and 3) pharmacologic control of the asthma is difficult. Other considerations include the quality of allergen vaccines available for treatment, ability of patients to comply, availability of facilities to treat untoward reactions, and the presence of underlying immunologic disease conditions and medications such as beta blockers [4]. A number of controlled trials showed that immunotherapy reduces the severity of allergic symptoms and medication requirements in children as well as adults [5•,6•,7,8••]. Today, even with the availability of a variety of pharmaceuticals to treat the symptoms of allergy, immunotherapy remains the only treatment that affects the natural course of the disease.

The 'Allergy March'

It is becoming clearer that the classic changes in allergen-specific IgG and IgE antibody levels during the course of immunotherapy are a manifestation of the process called "immune deviation," wherein the antibody shifts are regulated by changes in the activity of T_H1 and T_H2 cells [9]. In this model, allergen provocation in atopic subjects induces the production of IL-4, IL-13, and IL-5 by T_H2-type cells, causing B cells to switch to IgE synthesis. In addition, IL-5 promotes the differentiation, activation, and persistence of eosinophils in tissue sites. Immunotherapy reduces allergen-induced symptoms, production of inflammatory mediators, and nasal eosinophil and epithelial mast cell numbers. A rise in allergen-specific IgG ("blocking antibody") and a blunting of the seasonal rise in allergen-specific IgE titers also are hallmarks of immunotherapy. These characteristic changes may be due to the stimulation of T_H1 responses (*ie,* IL-2 and interferon-γ production), which promote IgG production by B cells, and/or to the induction of T_H2/T_H0 cell anergy, which diminishes T_H2 responses. These responses at the cellular and molecular levels serve as potential targets for new immunotherapy modalities.

The development of T_H1- and T_H2-type immune responses shortly after birth and during early childhood may determine the progression of allergic disease. Based on a prospective study following 216 children during the first 6 years of life, the incidences of allergic sensitization to inhalant allergens increased with age from 1.5% at the first year to 26% at 6 years [10•]. Marked increases in sensitization rates were observed mainly after the third year. A hypothesized reason for the global increase in allergic diseases is a failure in the natural conversion from the T_H2 to T_H1 phenotype due to a lack of antigenic stimulation in clean environments (the so-called hygiene hypothesis). An important question is whether immunotherapy can prevent this progressive disease or allergy march either by preventing sensitization to